Chapter 5

Essential Pharmacology, Therapeutics and Medicines Management for Non-medical Prescribers

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Learning objectives

After reading this chapter and completing the activities within it, the reader will be able to:

1 define key concepts of pharmacology
2 develop their own personal formulary
3 be aware of the complexities of pharmacology with specific reference to co-morbidity, medicine interactions, adverse medicine reactions and drugs with a narrow therapeutic index
4 appreciate concordant relationships compared with compliance with medication
5 understand the constituents of medicines management

Clinicians cannot know everything about all medicines but an essential element of safe prescribing practice is learning how to find out what you need to know, in order to prescribe safely the medicines that fall within your clinical practice. This chapter directs you to resources that you will use to develop and maintain knowledge about the medicines that you intend to prescribe. We guide you through processes, developed and evaluated as successful at the University of Central Lancashire, by which you will build your knowledge of pharmacology, therapeutics and medicines management to populate your own personal formulary.

The Textbook of Non-medical Prescribing, edited by Dilyse Nuttall and Jane Rutt-Howard.

Non-medical prescribing enables suitably trained and qualified practitioners to prescribe within their own competence and scope of practice (Health Professions Council 2007, Royal Pharmaceutical Society of Great Britain (RPSGB) 2007, Nursing and Midwifery Council (NMC) 2008). It is an essential component of the competence of prescribers (National Prescribing Centre (NPC) 2009) to have knowledge of both how the medicines that they prescribe work at their site of action and how the medicines are handled by the body.

Patients present with individual circumstances and the simplest scenario is that you will prescribe a medicine to an otherwise healthy person who is taking no other treatments. However, practitioners may find that this is the exception rather than the rule. This chapter directs you to resources, taking you through processes by which you can evaluate the significance of intention to prescribe, of co-morbidity and medicine interactions. Use of key resources will support you to work within your competence and determine the most appropriate course of action to: advise, prescribe, seek advice or refer.

Adverse drug reactions (ADRs), if undetected, account for significant levels of morbidity (even mortality) in patients, who can be subject to avoidable discomfort, distress or worse. In addition ADRs contribute to preventable medicine-related hospital admissions, which in 2004 were estimated to cost the NHS in excess of £500m annually (Pirmohamed et al 2004). This chapter directs you to resources and guides you through processes by which risks to patients from ADRs may be minimised.

Between a third and a half of medicines that are prescribed for long-term conditions are not used as recommended (National Institute for Health Clinical Excellence (NICE) 2009). Patients can pay a high price in unresolved illness and their own lost earnings, while the NHS wastes valuable resources. This chapter discusses issues of concordance and adherence, and guides you through processes by which negotiated consultations that result in mutual understanding are encouraged.

Maximising efficacy, minimising risks, reducing costs and respecting patients' choices are the main features of good prescribing of medicines (Barber 1995). 'Good prescribing' is supported by effective medicines management systems, where medicines management is defined as a system of processes and behaviours that determine how medicines are used by the NHS and patients (NPC 2002). This chapter discusses issues of medicines management, including how prescribing links to public health. You will be directed to resources and guided through processes to build your own medicines management support to aid safe prescribing arising from multidisciplinary teamwork.

Pharmacology as part of prescribing practice

As prescribers, you are required to 'understand the mode of action and pharmacokinetics of medicines, how these mechanisms may be altered (e.g. by age, renal impairment) and how this affects dosage' (NPC 2009). Non-medical prescribers are not expected to be pharmacologists and know everything about every medicine; however, they are required to understand the pharmacology of the medicines that they prescribe and the limits of their pharmacological competence, and apply this knowledge within their practice (NMC 2006).

Example of potential pharmacokinetic impact on patient care

Theory

Absorption is the process of medicine movement from the administration site to the systemic circulation. The amount and rate of absorption are determined by such factors as the physical nature of the dosage form, presence or absence of food in the stomach, rate of gastric emptying and concurrent administration with other medicines (Downie et al 2007).

Practice

The non-medical prescriber recognises the implications of diarrhoea and vomiting in the young woman taking oral contraceptives, because the rate of gastric emptying could affect absorption and hence whether therapeutic medicine levels necessary for contraception are maintained. Appropriate prescription and counselling advice is necessary to avoid an unplanned pregnancy.

Example of potential pharmacodynamic impact on patient care

Theory

Receptors are a target molecule that a medicine molecule has to combine with to produce a specific effect. β Blockers target β receptors and, in the cardiovascular system, relax blood vessels, slow down the heart rate and lead to an overall decrease in blood pressure (BP), which is beneficial. However, β receptors are also located in the lungs and bronchi where they help keep air passages relaxed and loose, an effect that could be antagonised by β blockers, leading to adverse effects on breathing. The Commission on Human Medicines has advised that β blockers, including those considered cardioselective, should not be given to patients with a history of asthma or bronchospasm (British Medical Association (BMA) and Royal Pharmaceutical Society of Great Britain (RPSGB) 2010).

Practice

The non-medical prescriber recognises that the patient presenting for review of BP management has been started on a salbutamol inhaler following atenolol dose increase. Blockade of β receptors in the lungs causes airway structures to become more tense and constricted, adversely affecting breathing in susceptible patients. Alternative BP management is necessary to relieve patients' breathlessness, without recourse to salbutamol.

These examples are cited to illustrate the importance, for patients, of prescribers applying an understanding of pharmacokinetics and pharmacodynamics to their clinical practice. The area that prescribers work within will determine the level of understanding of the medicines, within their personal formulary and scope of practice.

Brief introduction to pharmacological terms

To make sense of pharmacology it is necessary to refresh your understanding of physiology, because knowledge of the function of the organs and circulatory systems

and the human cell is essential when making sense of how body systems handle medicines (pharmacokinetics) and where at a cellular level medicines may act (pharmacodynamics).

Activity box 5.1

ACTIVITY

Refresh your physiology knowledge and understanding of key physiological concepts including: the human cell, mechanisms of the gastrointestinal and circulatory systems, and the functions of the kidneys and liver.

This chapter does not seek to replicate what is defined in detail in the many pharmacology books available, so it gives only brief summaries of pharmacological terms. It is, however, essential that you recognise the significance of understanding pharmacological concepts in the context of the prescribing care for your patients.

Pharmacokinetics

Pharmacokinetics is what the body does to the medicines. For almost all medicines the magnitude of the pharmacological effect depends on its concentration at its site of action. This phrase is simple enough! What it means is that for a medicine to have its effect it needs to be absorbed, e.g. through skin, bronchi or gastrointestinal tract, and then distributed in sufficient quantity to its site of action, usually via blood circulation. The active medicine will not remain in the body indefinitely but will be broken down or metabolised in order to be excreted or removed. Any of the above pharmacological processes may be affected by individual patient characteristics, e.g. liver or kidney function.

Texts and reference material that discuss pharmacokinetic concepts use such terms as: absorption, bioavailability, first-pass metabolism, distribution, protein binding, metabolism, cytochrome P450, excretion, half-life.

Put simply, **absorption** is the process of drug movement from the administration site to the systemic circulation (Figure 5.1).

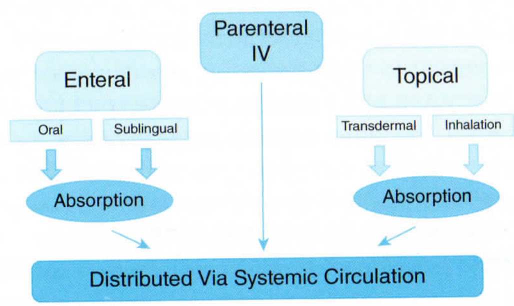

Figure 5.1 Routes of absorption.

The amount and rate of oral absorption are determined by several factors:

- Physical nature of the dosage form
- Presence or absence of food in the stomach
- Composition of the gastrointestinal (GI) contents
- Gastric or intestinal pH
- Mesenteric blood flow
- Concurrent administration with other drugs.

Most medicines are administered orally. Drug absorption is mainly in the upper small intestine, which is facilitated by the large surface area of microvilli and the rich blood supply. For drugs to pass across the lipid cell membrane they must be lipophilic, i.e. 'fat loving'. The level of mesenteric blood flow (arteries that supply blood to large and small intestines) directly affects the rate of removal of the drug from the site of absorption.

Gastric motility, constipation or diarrhoea affects the mixing in the GI tract which can alter the efficacy with which the medicines make contact with microvilli surfaces available to engage absorption. Alteration in the rate of gastric emptying will result in corresponding alterations in the rate of absorption, as in the case of diarrhoea or vomiting, which may affect whether therapeutic levels are achieved.

Activity box 5.2

Consider the effect on absorption of an analgesic or antiemetic if a patient had gastric stasis due to shock or migraine.

Consider what this may mean for the choice of route of administration and dosage form (see below) that a prescriber would select to ensure that adequate therapeutic levels could be achieved.

Dosage form refers to whether a medicine is in tablet, capsule or liquid form. The significance of the dosage form in prescribing practice is that it determines the rate and extent of absorption. Drugs in liquid dose form require no disintegration and often dissolution is already accomplished so absorption occurs more rapidly producing faster effects. For medicines administered as tablets or capsules, disintegration and dissolution of the released drug into the correct part of the GI tract are required for the drug to be adequately absorbed. Any alteration of the dosage form, e.g. crushing tablets or emptying capsules, affects the absorption process to one that has not been studied by the drug manufacturer. This should only be undertaken with expert advice where an alternative, licensed medication would not meet the patient needs (NMC 2006). Alteration of the dosage form or mixing of medicines before administration alters the pharmacokinetics of the product(s) and creates an unlicensed product (Medicines and Healthcare products Regulatory Agency (MHRA) 2009).

In 2009 the MHRA put in place changes to enable mixing of medicines before administration in clinical practice. These changes enable nurse and pharmacist independent prescribers to prescribe unlicensed medicines for their patients, on the same basis as doctors and dentists and supplementary prescribers, if part of a 'clinical management plan' (Department of Health (DH) 2009).

Bioavailability is the proportion of the administered dose that reaches the systemic circulation (Dale and Haylet 2008). It refers to the amount and rate of appearance of the drug in the blood, after administration in its initial dose form. Orally administered drug bioavailability is directly related to the individual solubility in body fluids:

Poor solubility = low bioavailability.

To produce a therapeutic effect, a drug must reach an adequate concentration in the blood. Drugs administered by the intravenous route are 100% bioavailable because they are administered directly into the blood; however, drugs administered by any other route will be less than 100% bioavailable, depending on the pharmacokinetic processes that affect them, such as first-pass metabolism.

First-pass metabolism is a defence mechanism whereby the liver protects the body from drugs (or toxins) absorbed via the GI tract by filtering them through a range of metabolic mechanisms, mediated by enzymes in the liver. All drugs taken orally, once they are absorbed, pass through the hepatic portal vein and can be subject to a degree of first-pass metabolism. As a result only part of the administered oral drug reaches the systemic circulation. This is called the 'first-pass effect'. Although there is patient variability, manufacturers take first-pass effects into account when developing appropriate dosage forms and recommending appropriate doses.

Activity box 5.3

Where in the *British National Formulary* (BNF) would you find clinicians guidance on prescribing for patients where liver disease compromises the first-pass effect?

Propranolol and verapamil are drugs that are subject to extensive first-pass metabolism.

- What does the BNF recommend about the prescribing of verapamil in liver disease?
- What does the BNF recommend about the prescribing of propranolol in liver disease?

Distribution

The systemic circulation distributes medicines across the body and can be affected by cardiac output and regional blood flow (Downie et al 2007), e.g. a warm patient would experience better blood flow and therefore improved drug distribution compared with a hypothermic patient. Inflamed tissue has increased vascularity and permeability and therefore increased passage of drugs.

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Body water is distributed into four main compartments: extracellular fluids including blood plasma, interstitial fluids, intracellular fluids, fluids within cells and transcellular fluids, such as cerebrospinal or synovial fluids (Dale and Haylet 2008). Drugs are usually distributed within each of these compartments in both free or bound form and move between compartments according to concentration. Only free drugs can be pharmacologically active, i.e. only free drugs can interact with their site of action to have an effect.

Protein binding

Drugs are bound by plasma proteins to a greater or lesser extent. The degree to which a drug binds to plasma proteins is determined by the drugs chemistry. The proportion of the drug that is bound to protein is pharmacologically inactive because the drug-protein complex is unable to cross cell membranes; however, this drug protein complex can quickly dissociate and release unbound drug into the system. The degree of protein binding will affect the intensity and duration of a drug's action.

A patient's condition and state of health may be an important consideration when thinking about protein binding because plasma proteins can be deficient in some diseases, e.g. in malnutrition, blood loss or liver disease (BMA and RPSGB 2010). Such patients could be subject to more of the drug being free to enter the tissue, and hence subject to toxicity despite a 'normal dose'.

Protein-bound drugs also provide a reservoir that may be displaced by adding another highly protein-bound drug, resulting, in a release of 'free' drug. This is a potential source of drug interactions. In practice this may be an important factor only in drugs that have high protein binding and a narrow therapeutic range, e.g. the 'fraction bound' of the anticoagulant warfarin is 97%; this means that, of the amount of warfarin in the blood, 97% is bound to plasma proteins (and is pharmacologically inactive) while the remaining 3% is the fraction that is active.

ACTIVITY

Activity box 5.4

Which BNF appendix offers the clinician guidance on drug interactions?

- Look in the relevant BNF appendix to identify which drugs interact with alcohol (ethanol).

Removal of a drug from the body occurs by two processes: metabolism and excretion.

Metabolism

Drugs are metabolised in the liver, lungs, kidneys, blood and intestines. The primary metabolic site is the liver. Metabolism is conversion of the chemistry of the drug, which requires enzymes, e.g. cytochrome P450 enzymes, to oxidise the drug (phase 1) or conjugate the drug (phase 2) in order to prepare it for excretion. The speed with which a drug is metabolised will determine the duration of the action of the drug. This, in turn,

will determine how often the drug is administered. If enzyme function is inadequate, metabolism can be compromised and cause toxicity, e.g. in liver disease, or very young or very old people. Metabolic enzymes can also be induced or inhibited by drugs that could affect the metabolism and therefore the duration of the drug.

Enzyme induction is a process by which a drug initiates or enhances the activity of an enzyme.

Enzyme inhibition is a process of interference or reduction in enzyme activity. Cytochrome P450 consists of the primary metabolic enzymes in the liver which can be subject to induction or inhibition from other drugs that the patient may take. See Table 5.1 for more information about the impact of enzyme inducers and enzyme inhibitors on cytochrome P450 enzymes.

ACTIVITY

Activity box 5.5

Where in the BNF can clinicians find guidance on prescribing for patients with compromised ability to metabolise drugs?

Look at the relevant BNF drug monographs to identify what steps are advised when prescribing paracetamol or statins to a patient with liver impairment.

Excretion

How the drugs are excreted can influence prescribing decisions. Most drugs are excreted in either the bile or the urine via the kidneys. Hence, renal function is important in determining excretion and patients with compromised renal function eliminate most drugs less effectively and are therefore at risk from toxicity. For drugs to be excreted in urine they need to become more hydrophilic (water loving or soluble) than lipophilic (fat loving or soluble). When lipid-soluble drugs pass through the kidneys they are reabsorbed in the distal tubule and return to the plasma. Some reabsorption of lipid soluble drugs occurs in Bowman's capsule; these are known as metabolites, and are often less

Table 5.1 Drugs affecting the action of cytochrome P450 enzymes (Thomson 2004)

CYP450 enzyme	Inducer (2-3 weeks)	Inhibitor (2-3 days)	Substrate
1A2	Cigarette smoke, omeprazole	Amiodarone, cimetidine, ofloxacin	Clozapine, haloperidol, naproxen, theophylline
3A4, 5, 7	Phenobarbital, St John's wort	Amiodarone, cimetidine, fluconazole, verapamil	Amlodipine, atorvastatin, erythromycin, methadone
2E1	Ethanol, isoniazid	Disulfiram	Ethanol, paracetamol, theophylline

active than their parent compounds, but in some drugs contribute to the overall effect of the drug, e.g. imipramine, propranolol and diazepam.

Excretion of drugs can be affected by the urinary pH, although this is of minor clinical significance because most weak acids and bases are inactivated by hepatic metabolism rather than renal excretion. Drugs that change renal blood flow can alter the excretion of other drugs. Renal blood flow is partially controlled by prostaglandins, so drugs that inhibit the manufacture of prostaglandins, such as non-steroidal anti-inflammatory drugs (NSAIDs) may inhibit the excretion of other drugs, e.g. lithium, leading to toxicity.

ACTIVITY

Activity box 5.6

Where in the BNF can you find guidance on prescribing for patients with compromised ability to excrete drugs?

Look at the relevant BNF drug monographs to identify what steps are advised when prescribing ibuprofen or tiotropium to a patient with renal impairment.

Half-life

Drug excretion is commonly expressed in terms of the half-life ($t_{1/2}$), which is the time required for the concentration of the drug in the plasma to decrease by half of its initial value. Concentration falls as a result of metabolism and excretion. Drug half-life is variable and can be long or short. Subsequent doses are given to raise the concentration levels to a peak and maintain therapeutic effect. The optimal dosage interval between drug administrations will be determined by the half-life of the drug. If dose interval is too long, the desired effect will not be achieved; too short an interval may lead to toxicity (Table 5.2).

Table 5.2 Example of effect of half-life ($t_{1/2}$), using drug with strength of 100 mg and a 6-hour half-life

Time (h)	Dose	Accumulated dose (mg)
0	1st dose 100 mg	
6	2nd dose 100 mg + 50 mg still present from 1st dose	150
12	3rd dose 100 mg + 75 mg still present from 1st + 2nd doses	175
18	4th dose 100 mg + 88 mg still present from 1st, 2nd + 3rd doses	188
24	5th dose 100 mg + 94 mg still present from 1st, 2nd, 3rd + 4th doses	194
30	6th dose 100 mg + 97 mg still present from 1st, 2nd, 3rd, 4th + 5th doses	197

As can be seen, accumulation becomes less at each dose as 'steady state' is achieved after three to five half-lives, whereby the amount of drug absorbed with each dose is balanced by the amount of drug metabolised and excreted.

Pharmacodynamics

Pharmacodynamics is the study of what the medicine does to the body when it arrives at its site of action and how drugs exert their effect at a cellular level. How can one drug affect breathing and another alter heart rate? The answer is in the **specificity** and **affinity** of an interaction between a drug and the biological target within the body.

The four main types of biological targets within the body are commonly categorised as follows.

Receptors, ion channels, carrier molecules and enzymes (Figure 5.2)

Receptors are proteins localised on the cell membrane or inside the cell. Any molecule that binds to a receptor to produce a specific effect is known as a *ligand*. Receptors and ligands must be compatible, like two pieces of a jigsaw, for binding and for a *specific* effect to occur. The strength of a molecule binding to the receptor site is known as *affinity*. A receptor has a high affinity for a molecule if it has a strong interaction, which enables binding and subsequent biological response to occur at very low concentrations. The receptors normally bind the body's own endogenous (originating from within the body) hormones and neurotransmitters, which in turn activates the receptor and leads

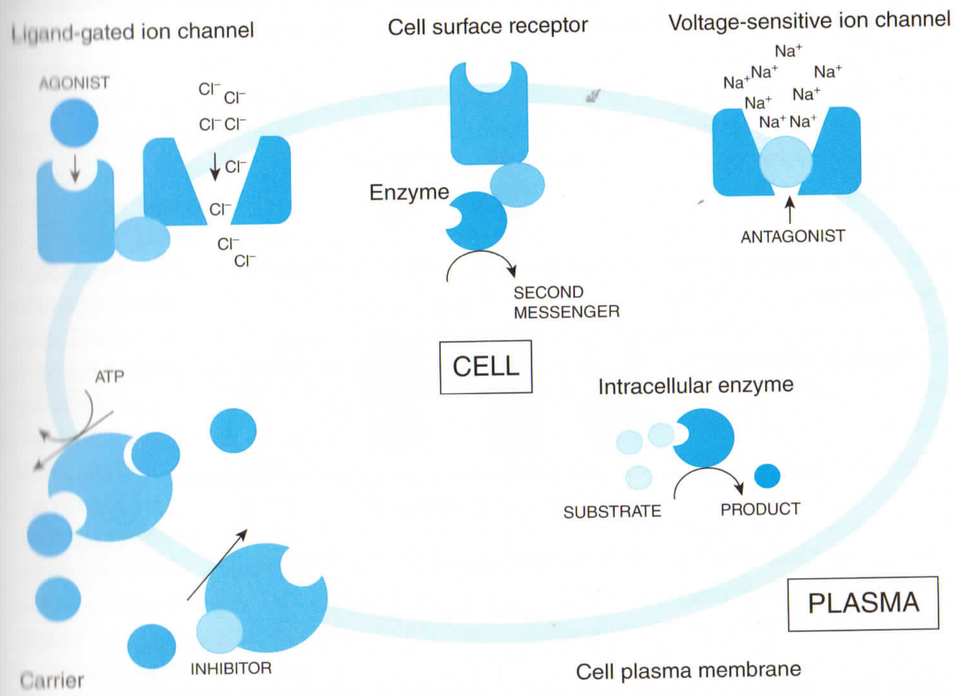

Figure 5.2 Types of targets for drug action.

to a physiological response, e.g. contraction, relaxation, secretion or enzyme activation.

If the drug's chemical structure or design is based on the structure of a specific receptor, it can selectively bind to the target receptor and produce a biological effect. The greater the specificity of the drug–receptor binding, the fewer the side effects likely to be encountered. The main types of action at receptor can be classified as receptor agonists and receptor antagonists.

An *agonist* is a drug that binds to a receptor and activates it, producing its normal biological response (Figure 5.3). An example of a receptor agonist is nicotine which is the primary alkaloid in tobacco products. It stimulates nicotinic acetylcholine receptors, naturally occurring in the body with receptors in the brain. The pharmacology of nicotine is complex, however, because it also acts as a receptor agonist in the peripheral and central nervous systems. Another effect of prolonged exposure to nicotine from tobacco smoking is a proliferation of receptors, leading to dependence and tolerance. Nicotine replacement products act as receptor agonists, which support smoking cessation by reducing cravings.

An *antagonist* is a drug that binds to a receptor without causing activation. The antagonist simply blocks the agonist from binding to the receptor and so inhibits the receptor's normal biological response (Figure 5.3). Examples of receptor antagonists include antihistamines such as loratadine and β blockers such as bisprolol.

The way that a medicine works is indicated in the nomenclature of the drug group to which it belongs, e.g. H_2-receptor antagonists block histamine H_2-receptors and antimuscarinic drugs block muscarinic acetylcholine receptors. Simply stating the facts does not, however, illustrate understanding of the pharmacology of these drugs, because it does not present the 'so what' of pharmacodynamics. If by this we mean if 'H_2-receptor

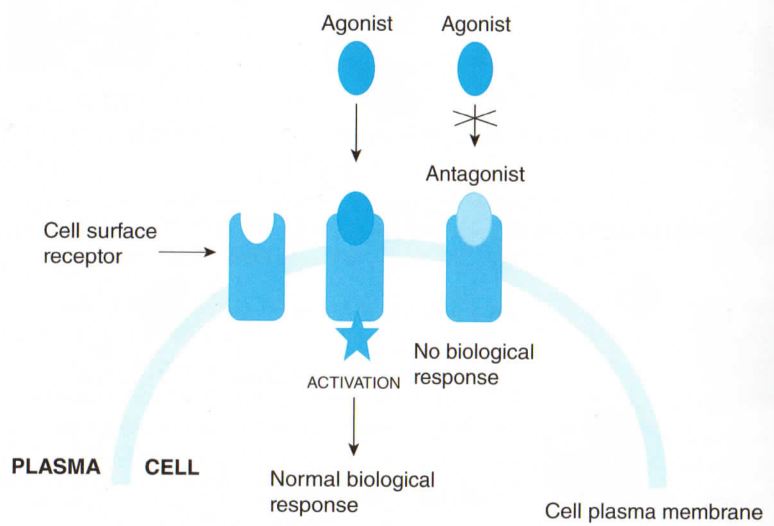

Figure 5.3 Action of the agonist and antagonist at cell surface receptors.

antagonists block histamine H_2-receptors' what does that mean for the patient? It means that the histamine H_2-receptors in the stomach which are stimulating gastric acid production are blocked, reducing the acid secretion, thus promoting healing of a gastric ulcer. As previously stated, you need to understand the pathophysiology in order to interpret the 'so what' of the pharmacology.

Activity box 5.7

If 'antimuscarinic drugs block muscarinic acetylcholine receptors' in the lung what does this mean for the patient's breathing?

Understanding the pharmacodynamics of drugs will enable you to understand and predict drug actions, interactions and toxicities.

Ion channels are gaps located in the cell plasma membrane that control the movement of electrolytes (specifically the free ions: sodium (Na^+), calcium (Ca^{2+}), potassium (K^+) and chloride (Cl^-)) in and out of the cell. There are several different types of ion channels; two of the most common ion channels targeted for drug action are the ligand-gated ion channels which are linked to a receptor and voltage-sensitive ion channels. The ligand-gated ion channels open only when the receptor is occupied by an agonist, whereas voltage-sensitive ion channels are gated by a different mechanism where the opening and closing of the ion channel are linked to voltage changes across the membrane.

When a drug behaving as a receptor agonist interacts with the receptor site at the *ligand-gated ion channels*, a conformational (or shape) change occurs and the channel opens. Large numbers of ions rapidly (milliseconds) enter the cell by moving down the electrochemical gradient; they flow from high ion concentration to low ion concentration, and initiate a biological response within the cell. A typical example of the normal biological function of this type of interaction is the action of the endogenous inhibitory neurotransmitter γ-aminobutyric acid (GABA) at the $GABA_A$ receptor on chloride channels. Drugs that act as agonists at GABA receptors or increase the amount of GABA produced commonly behave as anticonvulsants or anxiolytics, e.g. benzodiazepine tranquillisers facilitate chloride channel opening by acting at a specific benzodiazepine receptor coupled to the $GABA_A$ receptor. When the receptor is activated GABA neurotransmission is increased and chloride influx (or entry) increases, resulting in tranquillity.

Drugs can also bind directly to other parts of the ion channel, so when a stimulus arises the shape-changes that lead to the opening of the ion channel are blocked from occurring and the increase in permeability of the cell to ion influx is inhibited (or diminished). A typical example of this mechanism of drug action is the prevention of Na^+ influx by local anaesthetics, e.g. lidocaine binding to *voltage-gated channels*. The normal biological function of the voltage-sensitive ion channel is propagation (or multiplication)

of nerve impulses across an excitable cell membrane (e.g. nerve cell membrane) generated by temporary changes in voltage across the cell membrane via the opening and closing of the voltage-gated Na^+, K^+ and Cl^- ion channels. Blockade of Na^+ influx by local anaesthetics prevents propagation of the membrane action potential, blocks nerve impulses and hence prevents subsequent perception of painful stimuli.

Activity box 5.8

Drugs such as verapamil block the entry of Ca^{2+} at the L-type calcium ion channels in the heart, interfering with the cardiac nerve impulses and thereby reducing contractility.

Why is co-administration of verapamil with β blockers (antagonist at β adrenoceptors such as propranolol and atenolol) listed in BNF as a potential drug interaction?

Hint: think about the combined actions of these two drugs

Carrier molecules are proteins involved in the transport of endogenous molecules across cell membranes. These carrier proteins transport molecules that would otherwise be unable to cross the cell membrane, e.g. polar (or charged) hydrophilic molecules and ions that cannot permeate the lipid cell membrane. Carrier molecules are also involved in pumping ions out of the cell against a concentration gradient, a process that requires energy. There are many examples of the normal biological function of this type of carrier in the human body including:

- transport of glucose and amino acids into the cell
- transport of Na^+ and Ca^{2+} out of the cell
- transport of neurotransmitters into nerve cells
- active reuptake of ions and molecules from the kidney nephron back into the bloodstream.

The carrier proteins contain recognition sites which ensure that only specific molecules are transported. These recognition sites can be exploited as a drug target by designing drugs with structural similarity to the endogenously transported molecule, but instead the drugs modify or block the carrier, inhibiting transport. A typical example of a drug class that inhibits using this mechanism is inhibition of the noradrenaline transporter by tricyclic antidepressants (e.g. imipramine and lofepramine). The normal biological function of the noradrenaline transporter is inactivation of the neurotransmitter noradrenaline by reuptake of noradrenaline into the nerve terminal. Inhibition of this transporter therefore leads to an accumulation of the neurotransmitter noradrenaline in the nerve cleft, which can in turn activate adrenoceptors thought to be beneficial for the treatment of depression.

Activity box 5.9

Which pump does the drug omeprazole inhibit and how does this mechanism link to the action of omeprazole?

Hint: hydrogen ions are a necessary precursor required to form gastric acid.

Enzymes are proteins that catalyse (or accelerate) most of the normal functions of the cell and are therefore obvious drug targets for therapeutic intervention. Drugs could be targeted to inhibit enzyme function, which would lead to a decrease in the amount of a product formed. An example of this type of drug enzyme inhibition is the inhibition of angiotensin-converting enzyme (ACE) by captopril. Captopril prevents the conversion of angiotensin I into angiotensin II. Angiotensin II causes arteriolar constriction and an increase in diastolic and systolic blood pressure. Inhibiting the formation of angiotensin II in hypertensive patients will therefore result in a decrease in blood pressure.

If an enzyme is inhibited (or blocked) by a drug, the pharmacological effect could be due to accumulation (build-up) of the amount of enzyme substrate, if it cannot be converted into a product (a substrate is the substance on which the enzyme acts). An example of this mechanism of action is the inhibition of the enzyme acetylcholinesterase by neostigmine which leads to an accumulation of the substrate acetylcholine. More acetylcholine is therefore present and prolonging the action of acetylcholine enhances neuromuscular transmission in patients with myasthenia gravis (severe muscle weakness).

Activity box 5.10

Using the BNF identify which enzyme NSAIDs (e.g. aspirin, ibuprofen) inhibit.

Are the effects of NSAIDs due to enzyme substrate accumulation or a decrease the enzyme product formed?

A summary of some typical examples of drug action for each of the targets mentioned is given in Table 5.3.

Guide through processes to build and develop one's own formulary, with examples

Non-medical prescribers work in a diverse range of care pathways and the study of the pharmacology of the wide range of medicines that they may prescribe must logistically

Table 5.3 Examples of targets for drug action

Drug target		Effectors	
Receptors	**Type (subtype)**	**Agonists**	**Antagonists**
	Acetylcholine (nicotinic)	Acetylcholine, nicotine	
	Acetylcholine (muscarinic)	Acetylcholine, pilocarpine	Atropine, hyoscine
	Adrenoceptors (α/β)	Noradrenaline, adrenaline	Labetalol
	α_1-Adrenoceptor	Phenylephrine	Prazosin
	α_2-Adrenoceptor	Clonidine	
	β_1-Adrenoceptor	Dopamine, dobutamine	Atenolol
	β_2-Adrenoceptor	Salbutamol	
	Histamine (H_1)	Histamine	Promethazine
	Histamine (H_2)	Histamine	Cimetidine, ranitidine
	Dopamine (D_1 to D_5)	Dopamine, bromocriptine (D_2)	Phenothiazine derivatives, domperidone, metoclopramide (D_2), clozapine (D_4)
	Opiate (μ)	Morphine, diamorphine	Naloxone
	Oestrogen	Ethinylestradiol	Tamoxifen
	Epidermal growth factor receptor		Trastuzumab
	$GABA_A$	GABA, benzodiazepines, barbiturates	
	$GABA_B$	GABA, baclofen, tizanidine	
	Serotonin ($5HT_1$ to $5HT_5$)	Serotonin, sumatriptan, metoclopramide	Ergotamine, methysergide, ondansetron
Ion channels	**Type**	**Blockers**	**Modulators**
	Voltage-gated sodium channels	Local anaesthetics	
	Renal tubule Na^+ channels	Amiloride	Aldosterone
	Voltage-gated Ca^{2+} channels	Divalent cations	Dihydropyridines, opioids
	ATP-sensitive K^+ channels	ATP	Sulphonylureas
	GABA-gated Cl^- channels		Benzodiazepines

Table 5.3 *(Continued)*

Carriers	**Type**	**Inhibitors**	–
	Noradrenaline transporter	Tricyclic antidepressants, cocaine	–
	Weak acid carrier (renal tubule)	Probenecid	–
	$Na^+/K^+/2Cl^-$ co-transporter (loop of Henle)	Loop diuretics	–
	Proton pump (gastric mucosa)	Omeprazole	–
Enzymes	**Type**	**Inhibitors**	–
	Acetylcholinesterase	Neostigmine	–
	Cyclooxygenase	Aspirin	–
	Angiotensin-converting enzyme	Captopril	–
	HMG-CoA reductase	Simvastatin	–
	Phosphodiesterase type V	Sildenafil	–
	Dihydrofolate reductase	Trimethoprim, methotrexate	–
	Thymidine kinase	Aciclovir	–
	HIV protease	Saquinavir	–

5HT, 5-hydroxytryptamine; GABA, γ-aminobutyric acid; HMG-CoA, hydroxymethylglutaryl coenzyme A.
Adapted from Rang et al (2009) and Hopkins (1999).

be by self-directed study. Pharmacology textbooks are cited at the end of this chapter as suggested resources; the best pharmacology references for explaining these concepts and how your personal formulary drugs work are the books that make sense to you! Beyond the BNF and textbooks, there are a number of resources to help prescribers deepen their pharmacological understanding and update their knowledge, including higher education modules and courses, journal articles, e-learning resources and professional expertise such as pharmacist advice.

Summaries of product characteristics (SPC), which often include a description of the pharmacokinetic and pharmacodynamic properties of individual drugs, can be found on the Electronic Medicines Compendium which is available on the internet at the following link: www.medicines.org.uk/EMC/default.aspx

Community practitioner nurse prescribers work to a restricted formulary of preparations, which limits the choice of which medicines to study in order to develop understanding of pharmacology. However, the principle remains the same, which is to become familiar with the pharmacology of the products that you intend to prescribe.

Activity box 5.11

How should you select the appropriate medicines to study and populate your formulary?

Non-medical prescribers should reflect on:

- own area of practice
- the supporting guidelines
- any relevant local trust policies and formularies.

When you begin this process you may encounter the expression in textbooks: 'the pharmacology of this medicine is not well understood'; this is the case for a variety of medicines used empirically (historically). This is a signal to find a different example that will advance your understanding, because the pharmacology of many medicines is well understood. To start with, identify medicines from your clinical practice and, using suitable reference sources, develop an overview that represents *your* understanding of the pharmacokinetic and pharmacodynamic properties of the medicines.

Example 1

A non-medical prescriber working in a hypertension clinic in primary care would need to initially become familiar with the pharmacology of the medicines recommended for first-line use by the NICE hypertension clinical guideline (NICE 2006). Within this wide therapeutic area, the logical starting point would be with the formulary choices of their employing organisation, e.g. *bendroflumethiazide*, amlodipine, ramipril, candersartan, doxazosin.

Pharmacokinetic properties

Bendroflumethiazide is taken orally and completely absorbed from the GI tract. It is extensively metabolised with approximately 30% excreted unchanged in the urine. After an oral dose the onset of diuretic action is within 2 hours with the peak effect between 3 and 6 hours after administration. The duration of the diuretic action of bendroflumethiazide is between 18 and 24 hours. The onset of the hypotensive action is within 3 or 4 days.

Pharmacodynamic properties

Bendroflumethiazide is a thiazide diuretic that reduces the absorption of electrolytes from the renal tubules in the kidneys, thereby increasing the excretion of sodium and chloride ions, and consequently of water. Thiazides have a hypotensive effect, due to a reduction in peripheral resistance, and they enhance the effects of other antihypertensive agents.

Having gained an understanding of how one medicine works, repeat the process for the other medicines that you will commonly encounter or prescribe.

Talk to colleagues about what you have learned! Many of our students found the experience of going through this 'research' and personal formulary building process, and then explaining the pharmacology to their peers, extremely useful in consolidating and expanding their knowledge and application of pharmacology.

Understanding the pharmacokinetics and dynamics of medicines that you may prescribe is the first step, but there is greater knowledge needed of the medicines that you intend to prescribe than just the pharmacokinetics and pharmacodynamics. For each medicine, you should also use suitable reference sources to develop your knowledge of:

- indications for which the medicine may be used
- any pre-existing medical conditions that may influence the choice of medicine
- any adverse medicine reactions associated with the medicines
- any concomitant medicines that may have serious interactions
- education points for patient or family on use of medicines.

Example 2

A non-medical prescriber working in the care of painful diabetic neuropathy would need to become familiar with the pharmacology of the medicines outlined in the NICE Clinical Guideline 96: *Neuropathic Pain – Pharmacological management* (NICE 2010). The prescriber would study *duloxetine*, amitriptyline, pregabalin, tramadol, topical lidocaine.

Pharmacokinetic properties

Duloxetine is taken orally and is well absorbed from the GI tract with peak blood concentration occurring 6 hours after the dose. Food can delay the rate of and also has a slight effect on the extent of absorption but the manufacturers report that these effects have no clinical significance. Duloxetine is highly bound to plasma proteins. Plasma protein binding is not affected by renal or hepatic insufficiency. Duloxetine undergoes extensive biotransformation, metabolites being excreted mainly in the urine. Cytochromes involved in metabolism are CYP450-2D6 and -1A2. The elimination half-life of duloxetine ranges from 8 h to 17 h.

Pharmacodynamic properties

Duloxetine inhibits the uptake of both serotonin (5-hydroxytryptamine or 5HT) and noradrenaline (NA). The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system (CNS). In pre-marketing clinical trials, 50% of people experienced a 50% reduction in pain using pain assessment tools over a 12-week period. Patients not experiencing pain reduction of 30% within 60 days were unlikely to reach that level during further treatment.

Side effects

Due to the pharmacodynamic actions of duloxetine within the CNS it has a wide range of side effects that the non-medical prescriber should be aware of and should consider in relation to the individual patient each time that it is prescribed. Duloxetine should be used with caution in patients with a history of mania, a diagnosis of bipolar disorder or

a history of seizures. Duloxetine has also been associated with increased BP which can develop into clinically significant hypertension, so appropriate monitoring must be in place and due consideration taken of the potential effects of duloxetine should any changes in BP arise through treatment; for the supplementary prescriber monitoring of BP should form part of the review process for duloxetine detailed in the clinical management plan.

Drug interactions

Duloxetine potentially interacts with several medications. Due to its potential for causing dyspepsia possibly even gastric bleeding, other drugs that have a similar pharmacodynamic effect, such as NSAIDs, should be used with caution or it may be appropriate to advise on other analgesia such as paracetamol. Pharmacokinetic interactions of duloxetine include the inhibition of its metabolism by ciprofloxacin.

Education points for patient and family

The prescriber should be in a position to counsel the patient on the key issues surrounding the use of duloxetine and all the other drugs prescribed from his or her formulary. Counselling would start at the correct doses and administration times and move on to cover the main side effects to look out for; duloxetine may cause nausea and so the patient could be advised to take with food to combat this - it has been shown above that, although food delays absorption of the drug, it is not clinically significant and so this would be appropriate advice to give. Patients should be advised of potentially serious side effects that would warrant medical attention, such as the development of gastric discomfort or dyspepsia. Clinically significant drug interactions should also be covered such as that between duloxetine and ciprofloxacin; this may be an issue if the patient receives acute medical attention from a practitioner who is not normally familiar with the patient.

The process of developing knowledge of the drugs within your personal formulary will enable you to prescribe those drugs in a safe and appropriate manner and also to be able to discuss key points surrounding their use with other healthcare professionals and patients.

You will need to research, understand, update and apply the knowledge of the medicines in your personal formulary to ensure safe prescribing practice (NPC 2001, 2003, 2004a, 2004b, 2006).

BNF: practise using this essential resource

An essential resource when prescribing is familiarity with using the BNF including the appendices, which provide invaluable information on medicine interactions, co-morbidities that affect medicine handling, such as liver and renal disease, and information on cautions when prescribing to women who are pregnant or breastfeeding.

Competent use of the BNF is an essential resource for prescribers, particularly invaluable when prescribing for patients taking other medications and with co-morbidities that affect their ability to handle medicines. You cannot underestimate the importance of using the BNF efficiently and effectively. You cannot memorise the contents of the BNF

but you should be familiar with its layout so that you can use it for reference, as necessary, to extract the information that you need in a timely manner.

There is a quiz on the book's website to help you become more familiar with the BNF (BMA and RPSGB 2010). Remember, it isn't about knowing all the answers but going through the process of using the BNF to find the answers.

Prescribing in co-morbidity

Co-morbidity matters to prescribers for a number of reasons and the first is that co-morbidity can affect how a patient's body handles medicines. Co-morbidity that affects absorption such as constipation or gastric surgery may affect the rate or amount of medicine entering the body, whereas co-morbidity that affects distribution, e.g. blood loss, poor circulation or shock, may affect active medicine reaching its site of action if blood flow is restricted.

Impairment of the liver or kidneys will impede a patient's ability to metabolise or excrete medicines. It is worth noting that some medicines are administered as pro-medicines and need to undergo metabolism to become active, e.g. ramipril. In this case, patients with impaired liver function may not achieve therapeutic levels if their liver is not able to convert the pro-medicine into active medicine.

More usually metabolism is the mechanism for breaking medicines down by enzymatic action in order to make them easier for the body to eliminate. Hence, patients with severely impaired liver function will be at risk from raised levels of circulating medicines, leading to possible toxicity.

Excretion via the kidneys is the main route of elimination for many medicines and co-morbidity that adversely affects patients' renal capacity will expose them to risk of increased circulating medicines, also leading to possible toxicity. Renal function declines with age and patients' ability to excrete medicines is a significant consideration when prescribing for elderly people.

The above briefly summarises why co-morbidity that impacts on pharmacokinetics, and the patient's handling of medicines, are key considerations when prescribing for patients.

Prescribers must consider the holistic needs of the patient before them and where patients have co-morbidity, reflect on their competence to evaluate where it may be appropriate to prescribe, seek advice or refer. Community nurse practitioner prescribers can take some comfort that the restricted formulary to which they work, with few exceptions, includes medicines considered safe for the indications where they are prescribed at usual doses. However, the scope and range of non-medical prescribing are vast, with non-medical clinicians prescribing within clinical competence in situations where, as examples:

- usually healthy patients, young and old, require treatment for minor conditions such as candidiasis and dry skin
- frail elderly housebound patients with multiple co-morbidities and complex polypharmacy medication regimens
- non-medical prescribers adjust doses of medicines with narrow therapeutic indices on neonatal or special care units.

Individual prescribers will need to reflect on their patient group, their personal formulary and their competence to recognise and adjust to presenting co-morbidities.

Co-morbidity and polypharmacy

Another reason to discuss co-morbidity is that patients present not only with the condition to be treated by the non-medical prescriber but also with other conditions requiring medication, which may be outside the competence of the non-medical prescriber.

When discussing co-morbidity it is useful to reflect on the scale of morbidity and the demographic changes that alter the nature of patients most frequently presenting in a modern NHS. Three out of five people aged over 60 have a long-term condition, which is over 15 million people in England (DH 2001). One in six adults in the UK has a mental illness at any one time (DH 1999). Cardiovascular disease kills more than 110 000 people in England every year (DH 2000) and 1.8 million people in the UK are diagnosed with diabetes (DH 2007).

The older population (those aged 65 and over) account for 18% of the population in the UK but for 45% of consumption of all drug prescriptions. The proportion of people aged 65 and over is projected to increase to 22% by 2031 (Office for National Statistics 2007). Given such trends, it is vital that prescribers take every opportunity to reflect on the appropriateness or otherwise of drug prescriptions particularly for elderly people.

Drug treatments need to be tailored to the individuals needs and this is especially so in the elderly population. Renal function declines with age and this can have a significant effect on the pharmacokinetics and pharmacodynamics of the drugs being used (as highlighted above). The distribution of body fat and water is altered in older people, resulting in increased risk of drug toxicity and accumulation of lipid-soluble drugs. Many acute hospital admissions of older people are due to medication side effects and drug interactions. Such side effects and interactions may lead to adverse events such as falls, postural hypotension, dehydration, confusion, gastrointestinal bleeds, or renal or heart failure.

The increased frequency of coexisting illnesses in elderly people places them at particular risk of drug-illness interactions, e.g. many elderly people have both renal impairment and osteoarthritis. NSAIDs used for pain relief can adversely affect renal function, potentially leading to renal failure. Indications for drug use may range from treatment of a condition to providing symptomatic relief or improving the quality of life. Prescribers need to maintain a careful balance, avoiding both excessive medication and under-medication.

Example 3

A non-medical prescriber working in a hypertension clinic, following NICE (2006) clinical guidance, would know that bendroflumethiazide is a first-line agent in the treatment of hypertension in patients aged over 55 years. Bendroflumethiazide 2.5 mg produces a near-maximal BP-lowering effect at this 2.5 mg dose. Increasing the dose confers no extra benefit in terms of BP reduction (a dose-response 'ceiling' effect) but increases the likelihood of adverse side effects on electrolytes, blood lipid and glucose levels. Bendroflumethiazide also affects uric acid levels and hyperuricaemia is a known side effect, which can lead to gout in susceptible patients. The prescriber would therefore take caution in selecting an antihypertensive drug for a patient who had previously had gout and would avoid bendroflumethiazide in this case.

Management and avoidance of drug interactions

Where patients are taking more than one medicine there is a potential for medicine interactions. These may be chemical, pharmacodynamic or pharmacokinetic in origin. Chemical medicine interactions occur where two medicines are chemically incompatible and can be particularly relevant when prescribing or administering medicines intravenously. BNF, Appendix 6 offers useful guidance for managing and avoiding chemical medicine interactions.

Pharmacodynamic medicine interactions occur where medicines that are pharmacologically similar or act at the same sites of action are given together. So, for example, medicines that act at the same receptors or target the same enzyme pathway may be subject to pharmacodynamic interactions. This can result in additive effects, e.g. alcohol and benzodiazepines given together may cause enhanced sedation. Alternative antagonism may occur when medicines have opposing dynamic actions or are competing at the same site of action, e.g. buprenorphine would compete with morphine at opiate receptors - leading to a pharmacodynamic interaction.

Pharmacokinetic interactions occur where the body processes of absorption, distribution, metabolism and excretion are affected.

Example 4

The non-medical prescriber is managing a patient with hypertension also treated with lithium for bipolar disorder. Lithium is a drug with a narrow therapeutic index used to treat bipolar disorder. The pharmacodynamic action of bendroflumethiazide on ion excretion causes the excretion of lithium to be reduced, so raising lithium blood levels, which if co-prescribed would put the patient at risk of lithium toxicity. The prescriber would therefore take caution in selecting an antihypertensive drug for a patient who was taking lithium and would avoid bendroflumethiazide in this case.

There is a quiz on the book's website to complement this section of the chapter.

ACTIVITY

Activity box 5.12

Consider how many medicines a person with advanced type 2 diabetes may be taking, *before* you assess him or her within your competence and consider prescribing for any other condition with which he or she presents to you.

Tight BP control is essential to reduce morbidity associated with diabetes, so your patient may be taking one, two or three antihypertensive treatments plus a statin to reduce the cardiovascular risk and metformin or similar to manage the hyperglycaemia.

Extended example

Here are some patient scenarios to practise your BNF skills. All scenarios are separate but relate to the same patient. Imagine that Angela is consulting with you, within your competency, with the expectation of a prescription. Select a medicine (any medicine) from your personal formulary and use the BNF to check whether it would be safe to prescribe in the three scenarios.

The information you have gathered during consultation is as follows:

Patient name: Angela Patient
Date of birth: 23.03.1974
Address: 17 Any Drive, Anytown, Anywhere
Occupation: shop assistant
Married with one child
Current prescription: phenytoin
Past medical history: one full-term birth, 5 months ago
Past surgical history: none
Allergies: penicillin

Activity box 5.13

ACTIVITY

Scenario 1: Does the fact that she is taking phenytoin affect the choice of medicine that you were intending to prescribe?

You would need to check in the BNF, Appendix 1 whether there is a significant interaction between the medicine that you were intending to prescribe and phenytoin.

Activity box 5.14

ACTIVITY

Scenario 2: When you ask her if she is taking any over the counter/herbal medications, she tells you that she takes St John's wort.

Does this affect the medicine that you were intending to prescribe?

You would need to check in the BNF, Appendix 1 whether there is a significant interaction between the medicine that you were intending to prescribe and St John's wort.

Are there any other medicine-related issues that may concern you?

You need to consider carefully how you may advise Angela, within your competence, whether you would need to refer her to a colleague.

Activity box 5.15

ACTIVITY

Scenario 3: When you ask her if she may be pregnant, she tells you no because her last menstrual cycle was 1 week ago and was normal; she is, however, breastfeeding.

Does this affect the medicine that you were intending to prescribe?

You would need to check in the BNF, whether the medicine that you were intending to prescribe is safe to use in breastfeeding mothers.

Are there any other medicine-related issues that may concern you?

You need to consider carefully how you may advise Angela, within your competence, whether you would need to refer her to a colleague.

Management and avoidance of adverse medicine reactions

No medicine is risk free. All have one or more 'unwanted effects' in addition to the effect that is desired, e.g. would you want to take a medicine that had the following unwanted effects: rashes and blood disorders, which include thrombocytopenia (reduced number of platelets), leucopenia (low white blood cell count) and neutropenia (low level of neutrophils, a type of white blood cell)? You have probably taken this medicine many times in the past without giving any thought to what the unwanted effects might be. The medicine is paracetamol!

The usual term by which these unwanted effects is known is 'adverse drug reactions' or ADRs and is defined as 'A response to a drug which is noxious and unintended, which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' by the World Health Organization (WHO 2002).

Confusion arises due to another common term that is often used interchangeably with ADRs and this is the term 'side effect'. This term is used in the BNF. The WHO (2002) has defined side effects as 'Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug'.

The main difference between the two terms is that ADRs are always adverse or harmful to the patient taking the medicine, requiring discontinuation of the drug, whereas not all side effects are harmful, e.g. doxazosin may be prescribed in benign prostatic hyperplasia to relieve urinary retention but as a side effect may help a hypertensive patient by also reducing their BP.

Activity box 5.16

Look in the BNF at the Commission on Human Medicines' warnings for the following drugs: carbimazole, methotrexate, NSAIDs, the antibiotics - quinolones, trimethoprim, sulphonamides and flucloxacillin - varenicline and statins.

What action does the BNF say to take if a patient experiences the following ADRs associated with the given medicines?

- Severe muscular symptoms with statins
- Jaundice with ACE inhibitors
- Severe nausea due to nitrofurantoin
- Severe erythema and itching due to antifungals
- Liver cirrhosis with methotrexate
- Hepatotoxicity with amiodarone.

Sometimes precautions can be taken to prevent an ADR from occurring, e.g. use of sunscreen to prevent phototoxicity due to amiodarone or provision of a spacer device to prevent oral thrush due to inhaled steroid use in people with asthma.

Side effects are usually milder than ADRs and may be managed without having to discontinue the medicine, e.g. constipation as a result of opioid use can be managed with a laxative; dry mouth associated with some drugs, e.g. tricyclic antidepressants, can be managed with saliva replacements; and antimuscarinic drugs such as orphenadrine and procyclidine can be used to treat the symptoms of drug-induced parkinsonism due to antipsychotics.

Sometimes some side effects can also prove clinically useful, e.g. the constipating effect of codeine can be used to manage diarrhoea; in palliative care, hyoscine is used to treat drooling due to its antimuscarinic action, which causes dry mouth; and erythromycin, which can cause diarrhoea due to stimulation of motilin receptors, can be used to stimulate gut motility in critically ill patients.

The consequences of ADRs

As previously stated ADRs are harmful. They are responsible for a significant number of hospital admissions, inpatient morbidity, mortality and associated economic costs to the NHS (Pirmohamed et al 2004).

What do prescribers need to know?

- Factors that can influence the chance of a patient experiencing an ADR
- Steps to determine whether a drug is responsible for an ADR
- Pharmacovigilance and the reporting of ADRs.

Influencing factors

Impaired renal function

Reduced renal function can lead to the increased experience of ADRs in patients. Reduced renal excretion of the drug will give rise to accumulation of the drug in the body, leading to toxicity. This is especially serious when prescribing drugs with a narrow margin between the therapeutic and toxic dose (see below for more detail) and where renal function is the most important determinant of dosage, e.g. digoxin, which will require a reduced dose. Sensitivity to drugs may increase, so extra caution is required when prescribing nephrotoxic drugs such as NSAIDs, ACE inhibitors and methotrexate. Also, many side effects are poorly tolerated by patients with renal impairment.

Liver impairment

Changes in liver metabolism can also affect the chances of experiencing ADRs; however, liver impairment has to be severe before important changes in drug metabolism occur. Hepatotoxicity is either dose related or unpredictable (idiosyncratic). Drugs that cause dose-related toxicity may do so at lower doses in the presence of hepatic impairment than in individuals with normal liver function. Some drugs that produce reactions of the idiosyncratic kind do so more frequently in patients with liver disease. Tolcapone, used for parkinsonism and rosiglitazone, used in type 2 diabetes, should be avoided in patients with liver disease.

As elderly people have reduced renal and liver function, they are more prone to ADRs and therefore care is required when prescribing for this age group.

Multiple drug therapy

People with multiple disease states will often be on many drugs that increase their chances of experiencing ADRs. There may be various contributory factors to this such as additive effects, e.g. use of the combination treatment of isoniazid, rifampicin and pyrazinamide, all of which are associated with liver toxicity when used in tuberculosis treatment; excessive drowsiness where more than one drug has sedative effects and prescribing warfarin with NSAIDs which can increase risk of GI bleeding.

There can also be increased potential for drug-drug interactions when taking multiple drug therapy which can lead to an increased incidence of ADRs, e.g. concomitant use of simvastatin with erythromycin increases the risk of the patient having myopathy (muscle pain and weakness); clarithromycin markedly increases digoxin levels and numerous cases of digoxin toxicity have been reported.

Multiple disease states, e.g. liver and renal impairment, make the patient more susceptible to ADRs (see above).

Special attention needs to be given to elderly people who are often on multiple drug therapy. Their treatment regimens need to be simplified and non-medical prescribers need to ensure that they are only taking medicines that they actually need.

Gender

In general women appear to be at greater risk of ADRs than men (Wiffen et al 2002). The reasons for this are not clear but contributing factors include gender-related differences such as hormonal and immunological factors as well as the pattern of medicine use. In relation to the common analgesic codeine, the BNF (BMA and RPSGB 2010)

advises: 'The capacity to metabolise codeine can vary considerably and lead to either reduced therapeutic effect or marked increase in side-effects.' This may be particularly important in breastfeeding mothers because there can be a risk of morphine (product of codeine metabolism) overdose in breastfed infants.

Disease states

We have already looked at renal and hepatic impairment. Examples of other disease states that can predispose to an increased experience of ADRs are: HIV-positive patients who have an increased rate of skin reactions with co-trimoxazole and antiretroviral drugs, and infectious mononucleosis (due to the Epstein-Barr virus) which greatly increases the risk of rash in patients given amoxicillin.

Ethnicity

Different racial groups have genetic differences that can affect how they metabolise drugs, e.g. glucose-6-phosphate dehydrogenase (G6PDH) deficiency is highly prevalent in individuals originating from most parts of Africa and Asia, and from Oceania and southern Europe (BMA and RPSGB 2010). Susceptible individuals could develop acute haemolytic anaemia on taking a number of common drugs, e.g. nitrofurantoin, quinolone antibiotics (refer to BNF, section 9.1.5 - BMA and RPSGB 2010).

ACTIVITY

Activity box 5.17

Find the following two drug entries in the BNF and match the entry under 'Cautions' to the correct drug: carbamazepine and isoniazid:

- Risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele in individuals of Han Chinese or Thai origin
- Increased risk of side-effects in people with a slow acetylator status

Steps to determine whether a drug is responsible for an ADR

Following three easy steps will help in determining whether or not a drug is the causative agent.

What is the timing between the start of the drug therapy and the reaction?

Some reactions can occur soon after starting drug therapy, e.g. allergic reaction to penicillin. However, some ADRs can occur after the course of the drug therapy has finished, e.g. in the case of flucloxacillin where cholestatic jaundice and hepatitis can occur up to several weeks after treatment has finished.

Does the reaction improve when the drug is withdrawn or the dose is reduced?

Most ADRs go away or improve if the causative drug is stopped, e.g. dry mouth and blurred vision due to tricyclic antidepressants and GI bleeding with NSAIDs. However, not all have this effect because damage such as renal or liver failure may continue long after the drug has been discontinued.

Is the ADR a known one?

Check the BNF or manufacturer's literature (e.g. the patient information leaflet inside the box of tablets) to see if there is any information about the ADR that the patient is experiencing.

Pharmacovigilance and the reporting of ADRs

Pharmacovigilance is the science of collecting, monitoring, assessing and evaluating reports from healthcare professionals and patients on ADRs with a view to identifying new information about the potential risks associated with medicines and preventing harm. Although all drugs undergo pre-marketing testing (clinical trials) this activity does not usually involve vast numbers of people - usually just a couple of thousand - yet millions of people may end up taking the new medicine. Therefore, not all ADRs of a new medicine may be detected during clinical trials. It is therefore important that a robust mechanism is in place post-marketing to ensure that information on the type and incidence of all ADRs is collected. In the UK this can be done using the Yellow Card scheme.

This scheme involves the completion by healthcare professionals and patients of a freepost Yellow Card (available at the back of the BNF or online at the MHRA website) which allows details of the suspected ADR to be recorded and the information sent to the MHRA which collates and processes all the information and disseminates it. Close attention needs to be paid to new drugs which are designated by an inverted black triangle symbol in the BNF (▼) and any ADR irrespective of severity needs to be reported to ensure that data are gathered and made available to other healthcare professionals.

ACTIVITY

Activity box 5.18

Have a look at the Yellow Cards at the back of the BNF and practise completing one using the following case scenario:

Mrs Edna Smith, DOB 8 August 8 1950. Commenced the drug VoArth tablets (once a day) for her arthritis. She experienced severe rash and itching, yellow discoloration of the skin 2 weeks later and was hospitalised. She was diagnosed as having suffered hepatoxicity due to VoArth. She had been prescribed paracetamol and codeine only for pain relief for her arthritis before.

Key points for prescribers

- Consider whether drug therapy is necessary - weigh up the risks and benefits.
- Always consider whether any new symptom that the patient is experiencing is an ADR of a drug that he or she is already taking.

- Pay special attention to 'at risk' groups, e.g. elderly people, or people with renal or liver impairment.
- When possible prescribe a drug with which you are familiar. If you are not familiar with the drug consult the product literature for more information.
- Check the patient's history to determine if he or she has any documented ADRs to drugs – avoid these. Ask the patient for information on this if no documentation is found.
- Ask the patient if he or she is taking any other medicines, including herbal, complementary and bought over the counter at the pharmacy or other retail outlet.
- Give patients clear information about their medicines, e.g. how to take them, what they may experience when taking them and what to do if they suffer any harmful experience.
- Check whether there are any specific monitoring requirements before prescribing, e.g. liver function, blood counts, etc.
- If you come across a suspected ADR or side effect ensure that you complete a Yellow Card and post it to the MHRA.

Drugs with a narrow therapeutic index or range

Drugs of narrow therapeutic index are drugs, e.g. lithium, theophylline, ciclosporin or digoxin, for which there is a small range between an effective dose and a toxic dose. This means that toxic effects may happen with small increases in plasma concentration of the drug. Metabolic factors that affect plasma concentration, such as changes in renal function or hepatic enzymes, could therefore lead to toxic levels. Prescribers should be aware of these possible effects and ensure that action is taken to prevent doses reaching damaging levels.

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is the process by which plasma levels of drugs of narrow therapeutic index are measured. This should be done only when there is a clear benefit which contributes positively to patient care, as is the case in lithium monitoring (BMA and RPSGB 2010). Situations when TDM may also be appropriate include when the patient's condition may be hard to distinguish from toxic effects of the drug, such as with digoxin therapy, or in patients with co-morbidities that are likely to affect metabolism, such as hepatic impairment.

Proprietary name prescribing

Prescribing medicines by generic name is usually considered best practice, for reasons of cost-effectiveness and ease of supply. However, there are a few medicines where bioequivalence between manufacturers cannot be guaranteed; it is recommended that these are prescribed by proprietary name, to ensure that the patient receives the same dose each time. Brand prescribing is particularly recommended for drugs with a narrow therapeutic index. The BNF (BMA and RPSGB 2010) gives advice for the specific drugs

affected, but common drugs with a narrow therapeutic index that should be prescribed by brand include theophylline, ciclosporin and lithium.

Example of problems associated with drugs of narrow therapeutic index:

Drug interactions

Theophylline is metabolised by the liver, by hepatic cytochrome P450 enzymes. Drugs that induce liver enzymes will increase the clearance of theophylline and lead to lower plasma levels. Patients who smoke metabolise theophylline more quickly than non-smokers, because chemicals in smoke induce cytochrome P450 enzymes. This means that smokers may require higher doses of theophylline to achieve a therapeutic effect; conversely dose reductions may be appropriate if the patient stops smoking, so as to avoid theophylline toxicity developing. Patients should be made aware of symptoms of toxicity, such as palpitations, headache, nausea and vomiting, and the BNF (BMA and RPSGB 2010) recommends prescribing theophylline by brand name, to ensure bioequivalence.

Co-morbidity

Digoxin is excreted via the kidneys; dosage adjustments should be considered in patients with impaired renal function which should be checked before initiation. Elderly patients are particularly at risk from digoxin toxicity because their renal function declines with age. Common symptoms of toxicity include nausea and vomiting, and patients should be warned to report if such symptoms develop.

Lithium

Lithium is excreted via the kidneys; lithium levels can be influenced by a range of factors. Reduced sodium levels can increase the toxicity of lithium, so use of diuretics should be avoided. Similarly, patients should ensure adequate fluid intake and avoid any significant dietary changes that may affect sodium levels. Toxic effects of lithium can be serious – neurological effects or even death. Other signs of toxicity include GI effects such as anorexia, nausea, vomiting and diarrhoea. Proprietary name prescribing and TDM of lithium levels should be available if lithium is prescribed.

Building concordance

A key element of the medicines management process, the achievement of patient safety, is ensuring that patients receive the appropriate medicine for their condition and that they take/use the medicine correctly, with the aim of curing or stabilising their condition. Until recently, this fundamentally meant that the patient had to be compliant with the treatment regimen prescribed. However, it is acknowledged that, despite the expectation that patients will comply with the prescribed treatment regimen, non-compliance is a significant problem within all therapeutic areas and across all patient

groups (Carter et al 2005). As such, it is now argued that the more collaborative approach of concordance is adopted (Bond 2004).

It is useful at this juncture to differentiate between the terms often used to debate the issues relating to concordance. There are three commonly used terms: compliance, adherence and concordance. The National Co-ordinating Centre for NHS Service Delivery and Organisation (NCCSDO 2005) defined these three terms in a manner that demonstrates their distinctions while highlighting their linkage (NCCSDO 2005, p. 12):

> **Compliance**: 'The extent to which the patient's behaviour matches the prescriber's recommendations'
>
> **Adherence**: 'The extent to which the patient's behaviour matches agreed recommendations from the prescriber'
>
> **Concordance**: '... focused on the consultation process, in which doctor and patient agree therapeutic decisions that incorporate their respective views ... stretches from prescribing communication to patient support in medicine taking'

It is clear from these definitions that there is a move from a behavioural focus to a process focus; this is reiterated in the work of Bond (2004) who emphasises the need to explore the processes used to reach therapeutic decisions rather than the decision itself. In its most basic form, concordance in relation to prescribing can be defined as 'reaching a decision regarding treatment together'. Of course, the decision may be that no treatment is required or appropriate, and may instead indicate a need for health education and/or referral.

To provide a more detailed explanation, Britten and Weiss (2004) identified the key components of concordance. The first key component identified is the need for the practitioner to enable the patient to express his or her views and for the practitioner to understand them. Britten and Weiss (2004) emphasise that the patient and practitioners are equal partners whose opinions and views should form the basis of an agreed management plan. This of course relies on the practitioner articulating their view in a manner that is conducive to this process. Ultimately, it remains the patient's decision whether or not to take the medicine(s) (Britten and Weiss 2004).

The patient's health beliefs and their relation to medicines are recognised as a key factor in making the decision not to take medicines (National Prescribing Centre Plus (NPC Plus) and Medicines Partnership Programme (MPP) 2007). However, it is also acknowledged that of those patients who fail to take their medicines as prescribed, a significant proportion do so unintentionally (NICE 2009). Adopting a concordant approach to prescribing will support the practitioner not only in reaching an agreement that the patient can use, but also in enabling patient understanding.

In considering the role of non-medical prescriber, it is clear that concordance is fundamental to the prescribing consultation. Therefore, it is essential that the practitioner is aware of the concordance process and the key factors that impact on the achievement (or not) of concordance. NICE (2009) provides guidance incorporating many of these factors, yet interestingly uses 'adherence' as the chosen term for its focus. In addition, NPC Plus and MPP (2007) provide a competency framework to assist practi-

Table 5.4 Concordance: skills and actions

Focus: explain to patient that the approach used focuses on *concordance*
Approach: adopt a *non-judgemental* approach
Concerns: elicit the *patient's* concerns about medicines
Establish: the level to which the patient wants to be *involved* in decision-making
Consultation and communication: adopt a style that enables *individual* patients to express their view comfortably
Active listening: *understand* the patient's view
Remember: the patient has a *choice* not to take medicines
Education and information: ensure that the format used (verbal, pictures, leaflets, etc.) is appropriate for the individual patient (consider language barriers) so that they are able to make an *informed* decision
Strategy: *agree* the most appropriate strategy, including review schedules; employ *flexibility* (Mnemonic devised by Dilyse Nuttall 2010)

tioners in developing the appropriate skills necessary to achieve concordance. Table 5.4 summarises, using the mnemonic 'FACECARES', the actions and skills that support and promote concordance, as identified by NICE (2009).

Activity box 5.19

Access the National Prescribing Centre Plus and Medicines Partnership Programme (2007) *A Competency Framework for Shared Decision-Making with Patients: Achieving Concordance for Taking Medicines* available at: www.npc.co.uk/prescribers/resources/competency_framework_2007.pdf.

Identify any areas or competencies that you feel you need to develop, and develop an action plan to enable you to address any issues identified.

Using the FACECARE mnemonic, reflect on and critically analyse a recent consultation where a prescribing decision was made.

Medicines management

Medicines management has many definitions and has been described as 'a system of processes and behaviours that determines how medicines are used by the NHS and patients' (NPC 2002). This is a broad subject but the essence of medicines management is a system that promotes maximum benefit and minimal risk, from medicines, for patients. When medicines management systems are well established and implemented, more patients receive better, evidence-based and safer care (NPC 2002).

Why is it a priority?

Being prescribed a medicine is the most frequent clinical service provided by the NHS (MeReC 2002). Medicines are important to public health, with millions treated with statins and antihypertensives to prevent morbidity and mortality. Medicines account for more than 15% of the NHS revenue and there is a requirement of all prescribers to maximise value for money, within a cash-limited system (MeReC 2002). Effective medicines management frees up resources, which means that NHS money can be used for the benefit of patients. Just as prescribers cannot be expected to understand the pharmacology of all drugs, prescribers cannot be expected to be experts in pharmacoeconomics or risk-benefit ratio analysis. One contribution that the prescriber makes to effective medicines management is familiarity with and application of relevant frameworks, formularies and guidelines.

Medication problems are implicated in 5-17% of hospital admissions, with medication errors accounting for 25% of all reported harm-related incidents (Pirmohamed et al 2004). It has been estimated that medicines-related hospital admissions cost the NHS £500 million a year in additional days spent in hospital. More important than the costs to manage these adverse drug-related events are the human costs of avoidable illness or mortality. Good medicines management, timely monitoring and review have been shown to prevent hospital admissions and improve patient safety.

There is also significant waste when medicines are not managed appropriately; currently half of all patients with chronic conditions do not use their medicines as intended. Obtaining accurate and timely information about patients' medicines, concordant consultations and regular medication review are all elements that constitute processes of medicines management. Patient decision aids are recently introduced tools, increasingly used within consultations, to enable patients to better understand the pros and cons of medicine taking.

Prescribers are encouraged to reflect on what constitutes 'good prescribing.' Whilst guidance may imply that a right answer always exists, prescribers should recognise the complex trade offs that have to be made between conflicting aims. Barber (1995) proposed 'four aims that a prescriber should try to achieve, both on first prescribing a drug and on subsequently monitoring and reviewing it. They are: 'to maximise effectiveness, minimise risks, minimise costs, and respect the patient's choices' (Barber 1995). New prescribers are encouraged to read this paper, because these aims, as well as the aims of medicines management, are as relevant today as they were back then.

Other resources to support your learning

Key textbooks

Dale MM, Haylett DG (2008) *Pharmacology Condensed*, 2nd edn. London: Churchill Livingstone.
Downie G, MacKenzie J, Williams A, Hind C (2007) *Pharmacology and Medicine Management for Nurses*, 4th edn. Edinburgh: Churchill Livingstone.
Rang HP, Dale MM, Ritter JM, Flower R (2007) *Rang & Dale's Pharmacology*, 6th edn. London: Churchill Livingstone.
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http://bnf.org/bnf/index.htm - *British National Formulary* (BMA and RPSGB)
www.medicines.org.uk/EMC/default.aspx - electronic Medicines Compendium, containing summaries of product characteristics (SPCs)
www.mhra.gov.uk/Aboutus/index.htm - MHRA

Key themes: conclusions and considerations

Public health	Antibiotics are a common drug prescribed by non-medical prescribers. There is proven research whereby it is evident that patients do not always complete their full prescription of antibiotics and that this is contributing to the issue of antimicrobial resistance Consider how, in relation to the concepts of compliance versus concordance, you can help facilitate your patient to complete their full prescription of antibiotics
Social and cultural issues	Cultural and ethnical differences have been shown to impact on the body's ability to 'handle' certain drugs Consider your learning needs in relation to cultural and ethical issues, and your clinical practice population and personal formulary
Prescribing principles	The prescribing principles are embedded within this chapter and especially in terms of 'considering the strategy'. Pharmacology knowledge of your personal formulary is paramount Consider how the risks of the chosen strategy can be alleviated, through a comprehensive knowledge base and the promotion of a concordant relationship with the patient

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Department of Health (2007) *NSF for Diabetes*. London: DH.
Department of Health (2009) *Non-Medical Prescribing Programme: Changes to medicines legislation to enable mixing of medicines prior to administration in clinical practice* (on-line). Available at: www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Prescriptions/TheNon-MedicalPrescribingProgramme/DH_110765 (accessed May 2010).
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Chapter 6
The Multidisciplinary Prescribing Team

Dawn Eccleston

Learning objectives

After reading this chapter and completing the activities within it, the reader will be able to:

1. discuss the meaning of the 'multidisciplinary prescribing team'
2. identify the roles of non-medical prescribers
3. critically analyse the importance of working as part of a multi-disciplinary team
4. discuss the benefits of the 'multidisciplinary prescribing team' for patients and clients
5. apply knowledge about multidisciplinary prescribing to non-medical prescribing practice

Defining 'the multidisciplinary prescribing team'

Non-medical prescribing is a rapidly expanding field of healthcare practice. From its constrained beginnings, when nurses were allowed to prescribe from a very limited list, the field of prescribing has now increased to include different professions and expanded to include complete use of the *British National Formulary* (BNF). To facilitate these changes and developments, there has been a distinct need for the teams in which non-medical prescribing has been undertaken to evolve. This chapter examines the meaning of 'multidisciplinary team working in prescribing' and looks at the various roles of the prescribing team members. It also considers the support processes that are provided to individual non-medical prescribers by different members of the team, in a variety of situations and circumstances.

Clark (2008, cited in Goodman and Clemow 2008, p. 140) defines a team as:

The Textbook of Non-medical Prescribing, edited by Dilyse Nuttall and Jane Rutt-Howard.

> ... a group of people with a high degree of **interdependence** geared towards the achievement of a **common goal** or completion of a **task** ... it is not just a group for administrative convenience. A group, by definition, is a number of individuals having some unifying relationship. Team members are deeply **committed** to each other's **personal growth** and **success**. That commitment usually transcends the team. A team outperforms a group and outperforms all reasonable expectations given to its individual members. That is, a team has a **synergetic** effect ... one plus one equals a lot more than two. Team members not only **cooperate** in all aspects of their tasks and goals, they share in what are traditionally thought of as **management functions,** such as planning, organizing, setting performance goals, assessing the team's performance, developing their own strategies to manage change, and securing their own resources.

Activity box 6.1

Consider the words in bold print in Clark's definition and answer the following questions:

Do these words represent the ideals of a good multidisciplinary team?
What is actually meant by the term 'multidisciplinary'?

Confusion in terminology

Various terms have been used to define professionals 'working together'. Many healthcare professionals will be familiar with terms such as 'multiprofessional', 'multiagency', 'multidisciplinary', 'interagency', 'interprofessional', 'collaborative' and 'partnership working'. Although the words have different meanings ('inter' meaning 'between or among', 'multi' meaning 'many'), they are often used and interpreted differently by individual professionals and different disciplines.

In the true sense of the term, interprofessional or interdisciplinary work means that there is collaborative working and/or working together, whereas multiprofessional or multidisciplinary work means that there is more than one profession working in the same area, or with the same patient or client, but not necessarily in a collaborative fashion (Leathard 1994). The terms are, however, often used interchangeably. Leathard (1994) suggests that the term 'interprofessional' suggests only that two groups are working together, whereas 'multiprofessional' or 'multidisciplinary' implies a wider group involvement. For the purposes of this chapter the terms are interchangeable. Therefore, as long as all members of the team know precisely what is meant, then team morale and patient/client care should not be compromised. In fact, effective multidisciplinary team working can, I suggest, enhance both patient and staff satisfaction!